UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,560	04/25/2005	Hong Liang	54785-0551 (299447)	7039

23370 7590 11/20/2007

JOHN S. PRATT, ESQ
KILPATRICK STOCKTON, LLP
1100 PEACHTREE STREET
ATLANTA, GA 30309

EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
11/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/070,560	LIANG ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *1-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/11/02,8/13/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Restriction Requirement:

Applicant's election, without traverse of Group II, claims 11-23, drawn to a method of purifying Endostatin protein, in the reply filed on 29 August 2007 is acknowledged.

Claims 1-23 are pending in the instant application. Claims 1-10 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 11-23 are under consideration.

Priority:

It is noted that this application claims priority to PCT/US00/25166, 14 September 2000, which claims benefit of 60/153,698, 14 September 2000. The specification should be amended to recite the priority claims in the first paragraph of the specification.

Information Disclosure Statement:

The Information Disclosure statements (IDS) submitted on the 11 June 2002, has been considered. Signed copy is attached.

The information disclosure statement filed 13 August 2002 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because reference 1 on page 1 of 7 has not been included among the papers filed with the instant application; the reference has therefore been lined through and the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the

statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Specification:

The use of the trademarks, such as Endostatin™, Streamline™ Sepharose™, and Toyopearl™, has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Rejections

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11, 15, 16, 18, 20 and 22 contain the trademark/trade name Endostatin™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claimed scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade

name is used to identify/describe Endostatin protein and, accordingly, the identification/description is indefinite.

Claim 11, the independent claim of the instant invention, is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: The claim does not recite the source of the Endostatin recited in lines 5, 8, and 9 of Claim 1. It is unclear if applicant intends to: (a) apply fraction eluted from first cation exchange column and apply it to a heparin-sepharose column; (b) apply fraction eluted from heparin-sepharose column and apply it to an anion exchange column; and (c) apply fraction eluted from an anion exchange column and apply to second cation exchange column. Furthermore, it is unclear if "a first cation exchange column and expanded bed chromatography" constitutes one or two method steps.

Claims 16, 21, 22, and 23 recite steps comprising lyophilizing Endostatin and reconstituting lyophilized Endostatin. Lyophilization and reconstitution do not comprise a purification method. It is therefore unclear how these claims further limit the method of claim 11.

Claims 12-14, 17, 19, and 20 are included in this rejection as dependent from rejected claims.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of purifying Endostatin comprising:

1. capturing Endostatin from a sample using a Streamline SP resin column or a SP-Sepharose Fast Flow resin wherein the Endostatin is eluted using an elution buffer

consisting of 17 mM citric acid, 66 mM Na phosphate, 250 mM NaCl, pH 6.3; collecting eluate from said column; and

2. applying the eluate from step 1 to a heparin-sepharose column or a column comprising a resin that selectively binds Endostatin in a hydrophobic interatction mechanism, wherein the Endostatin is eluted using an elution buffer consisting of 30% 20mM Tris, 50mM NaCl, pH 7.6, 70% 20mM Tris, 500 mM NaCl pH 7.6; collecting eluate from said column; and

3. applying the eluate from step 2 to an anion exchange column wherein said the Endostatin is eluted using an elution buffer consisting of 66 mM sodium phosphate, 17 mM citric acid, 250 mM NaCl, pH 6.3; collecting eluate from said column; and

4. applying the eluate from step 4 to a second cation exchange column, wherein the Endostatin is eluted using an elution buffer of 66 mM sodium phosphate, 17 mM citric acid, 250 mM NaCl, pH 6.3; and

5. further concentrating the Endostatin by pushing the sample collected in step 4 through a membrane and eluting Endostatin from the membrane with 17 mm Citric acid, 66 mM sodiumn phosphate, 59 mM NaCl, pH 6.2 and

6. Removing citrate by exchanging with PBS and SOS detergent

does not reasonably provide enablement for the full scope of the claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are broadly drawn to a method of purifying Endostatin protein comprising passing the sample through a series of chromatography columns: a first

cation exchange column, a heparin-sepharose column or a column containing a resin used for hydrophobic interaction chromatography, an anion exchange column, a second cation exchange column thereby concentration the Endostatin. Thus, the claims are drawn to a method using any type of recited column (cation exchange, resin used for hydrophobic exchange, anion exchange) and using any, unspecified buffer to eluate samples from said columns; the claims also recite removing citrate by exchanging with PBS and any detergent.

The specification teaches basic recovery process of Endostatin protein is accomplished using four chromatography steps and a final concentration and diafiltration step (page 21, lines 16-18). The first chromatography step, the Endostatin capture step, uses a specific resin Streamline-SP; other resins that act as cation exchangers may be used (page 21, lines 26-33). The specification is silent as to the elution buffer to be used in this step, teaching only that the protein is eluted from this column with salt (page 22, lines 18-20). The next chromatographic step is to apply the sample to a Heparin-Separose Fastflow column, or a column employing a resin appropriate for hydrophobic interaction chromatography (page 22, lines 21-29). The disclosure is silent as to the elution buffer to be used at this step in the process. The next step in the chromatographic process consists of two columns that are connected and run in tandem: a quaternary amine column (an anion exchange column) and an SP-cation exchange column (page 23, lines 25-28); the disclosure is silent as to the elution buffer to be used at this step in the process. The final step in the purification procedure is concentration and dialysis. The sample is pushed through a membrane with a molecular cutoff chosen to retain Endostatin protein. Several liters of formulation buffer are run over the membrane to recover Endostatin protein remaining in the filters (page 24, lines 12-21). However, the makeup of the formulation buffer is not disclosed. The specification also does not disclose appropriate buffers for the dialysis step. Thus, the specification provides guidance as to the type of columns to be used in the four chromatography steps, but does not provide sufficient guidance to one of ordinary skill in the art as to the types of buffers one should use in order to elute biologically active, soluble Endostatin. The art teaches, for example, that formation of a stable expanded

bed, a requirement for step one, depends on several parameters, among which are ionic strength and pH (Johansson et al. 1996. Journal of Biotechnology 48:9-14, page 10, 1st column, 2nd paragraph). Furthermore, this information is critical to the practice of the methods of the instant invention, since the specification teaches that during scale up of the Endostatin protein purification process of the instant application, it was determined that Endostatin protein precipitates under certain conditions (page 25, lines 5-7). In addition, one of ordinary skill in the art would not predict that addition of any, unspecified detergent to the PBS dialysis buffer would result in a biologically active, correctly folded protein, since it is routine in the art to remove detergents by dialysis.

The working examples (Examples 3-6 and 11) only provide one specific elution buffer for each of the four chromatography steps of the methods of the instant invention and one dialysis buffer of PBS and SOS. These buffers are disclosed above. Thus, the specification fails to teach the skilled artisan how to practice the claimed method without resorting to undue experimentation to determine the appropriate elution buffers to be utilized to elute biologically active, soluble Endostatin.

Due to the large quantity of experimentation necessary to determine the appropriate elution buffers to be utilized to elute biologically active, soluble Endostatin, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that establishments the criticality of ionic strength and pH in conducting expanded bed chromatography, and the breadth of the claims which fail to recite any elution buffers, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 U.S.C. § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-13, 15, 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dhanabal et al. (1999. Cancer Res. 59:189-197, cited on IDS of 11 June 2002) in view of Johansson et al. (1996. J Biotechnology 48:9-14) and further in view of Goldstein et al (1999. US 5,861,295, the '295 patent).

Dhanabal et al teach the expression of recombinant mouse Endostatin in *Pichia. Pastoris.* Large scale production and purification of the recombinant protein was carried out. Initial steps of a purification process comprise centrifugation and concentration of crude supernatants by ammonium sulfate precipitation, solubilization of precipitate, dialysis, ultrafiltration and chromatography on a heparin-sepharose column. (page 190, 1st column, last paragraph, bridging 2nd column 1st paragraph). Johansson et al. teach a method of large scale recovery and purification of recombinantly produced protein comprising growth of cells expressing a target protein (page 10, 2nd column, 1st paragraph), applying cell suspension to an expanded bed cation exchange STREAMLINE DEAE column (page 10, 2nd column, section 2.2). Further purification was performed using a Phenyl Sepharose Fast flow column, followed by chromatography on an anion exchange column (page 10, 1st column, 4th paragraph). Johansson et al teach that using expanded bed and rigid monodisperse ion exchange medium is fast and efficient recovery and purification. Among the advantages is that this process can be implemented where a protein needs to be isolated from a crude cell suspension (such as that taught by Dhanabal et al.) or cell homogenate. The use of

expanded bed should be considered as an alternative to processes such as centrifuguation, filtration, ultrafiltration and ammonium sulfate precipitation (page 14, section 3.2). The '295 patent teaches purification of recombinant proteins by anion or cation exchange chromatography, hydrophobic interaction chromatography (column 9, lines 27-30). The reference teaches concentration by diafiltration and subsequent lyophilization. The '295 patent teaches that the multiple step prevent the contamination of proteins during the purification process (column 4, lines 20-25. Given that Johannsson et al. teach a method of large scale recovery that uses expanded bed chromatography as an alternative to centrifugation (taught by Dhanabal et al). and the advantages of said method followed by Phenyl Sepharose Fast flow column, followed by chromatography on an anion exchange column for further purification and the '495 patent teaches multiple purification steps offer advantages of purifying proteins without contamination during the process, it would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Dhanabal et al and purify the recombinant endostatin (taught by Dhanabal) using the chromatography methods taught by Johansson et al and the chromatography and ultrafiltration methods taught by the '295 patent and store the purified Endostatin by lyophilization, as taught by the '295 patent. One would have anticipated success, because all these methods are well known in the art.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dhanabal et al., Johansson et al, and the '295 patent as applied to claim 11 in view of Hjorth (1997. TIBTECH 15:230-235). The teachings of Dhanabal et al., Johansson et al (1996. J Biotechnology 48:9-14), and the '295 patent are outlined in detail above. The references, individually or combined, do not teach a method of purifying Endostatin wherein the first cation exchange column contains Streamline sulfopropyl resin. Hjorth reviews expanded bed chromatography for production of recombinant proteins. Among the commercially available purpose designed products, marketed under the trade name STREAMLINE is an SP resin (agarose-quartz sulfopropyl resin). Thus, it would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made

to modify the teachings of the above references, and substitute one commercially available STREAMLINE product for another. One would have been motivated to make the substitution and have anticipated success, because Hjorth teaches both resins are used for expanded bed chromatography

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dhanabal et al., Johansson et al, and the '295 patent as applied to claim 11 and 15 in view of Davis (1990. US 4,919,811, the '811 patent). The teachings of Dhanabal et al., Johansson et al, and the '295 patent are outlined in detail above. The references, individually or combined, do not teach a method of purifying Endostatin wherein the membrane is made of polyethersulfone. The '811 patent teaches membranes made of polymers, said membranes are employed for binding specific biological material such as proteins. The membranes are made of polyethersulfones (column 1, lines 13-30). Thus, it would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of the Dhanabal et al., Johansson et al, and the '295 patent, and utilize a membrane made from polyethersulfone. One would have been motivated to utilize said membrane and anticipate success because the '811 patent teaches that a membrane of polyethersulfone provides specific binding capacity for proteins of interest.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dhanabal et al., Johansson et al, and the '295 patent as applied to claim 11 and 15, in view of Chang et al. (1987. US 4,666,865, the '865 patent). The teachings of Dhanabal et al., Johansson et al (1996. J Biotechnology 48:9-14), and the '295 patent are outlined in detail above. The references, individually or combined, do not teach a method of purifying Endostatin wherein the elution buffer comprises a citrate-phosphate buffer. The '865 patent teaches that 0.1M citrate-phosphate buffer is a suitable elution buffer for eluting protein (IFN-gamma). Thus, it would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of the above references, and utilize a citrate-phosphate elution buffer to elute proteins off of a

membrane, since the '865 protein teaches that citrate phosphate buffer is appropriate as an elution buffer for protein purification. One would have anticipated success, because the '865 patent teaches citrate-phosphate buffer as a suitable elution buffer.

Claims 20-23 are free of the prior art. While the art teaches that one can remove virtually any component by exchanging with virtually any buffer, for example one can dialyze against virtually any buffer and remove virtually any component as long as all components of the buffer and the component(s) to be removed are smaller than the pore size of the dialysis tubing used, there is no teaching in the art of a method comprising removal of citrate by exchanging with phosphate buffered saline and a detergent.

Art made of record:

The following art is made of record and not relied upon is considered pertinent to applicant's disclosure.

Trinh et al (2000. Bioseparation 9:223-230) teach a method of recovery of mouse endostatin from *P. pastoris* using expanded bed adsorption (STREAMLINE SP XL) followed by gel filtration on a Superdex 75 column. Shiloach et al (2003. J. Chromatography B 790:327-336) teach Endostastin capture from *P. pastoris* culture using expanded bed chromatography. The reference teaches a method of evaluating four different experimental conditions for further purification steps. However, neither of these references are available as prior art, since the publication date of both of these references are after the effective filing date of the instant application, which is 14 September 1999.

Conclusion:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. H. S./

/Manjunath N. Rao, /
Supervisory Patent Examiner, Art Unit 1647